DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee; Notice of Meeting

Pursuant to Public Law 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee on December 4–5, 1995. The meeting will be held at the National Institutes of Health, Building 31C, 6th Floor, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892, starting on December 4, 1995, at approximately 9 a.m., and will recess at approximately 5 p.m. The meeting will reconvene on December 5, 1995, at approximately 8:30 a.m. and will adjourn at approximately 5 p.m. The meeting will be open to the public to discuss Proposed Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496) and other matters to be considered by the Committee. The Proposed Actions to be discussed will follow this notice of meeting. Attendance by the public will be limited to space available. Members of the public wishing to speak at this meeting may be given such opportunity at the discretion of the Chair.

Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone (301) 496–9838, FAX (301) 496–9839, will provide materials to be discussed at this meeting, roster of committee members, and substantive program information. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable recommendations, should contact Dr. Wivel in advance of the meeting. A summary of the meeting will be available at a later date.

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: November 9, 1995.

Susan K. Feldman,

Committee Management Officer, NIH.

[FR Doc. 95–28244 Filed 11–14–95; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Proposed Actions Under the Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, amended 60 FR 20726).

SUMMARY: This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, amended 60 FR 20726). Interested parties are invited to submit comments concerning these proposals. The proposals will be considered by the Recombinant DNA Advisory Committee at its meeting on December 4–5, 1995. After consideration of these proposals and comments by the Recombinant DNA Advisory Committee, the Director of the National Institutes of Health will issue decisions in accordance with the NIH Guidelines.

DATES: Comments received by November 27, 1995, will be reproduced and distributed to the Recombinant DNA Advisory Committee for consideration at its December 4–5, 1995, meeting.

ADDRESSES: Written comments and recommendations should be submitted to Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, or sent by FAX to 301–496–9839.

All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX to 301–496–9839.

SUPPLEMENTARY INFORMATION: The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

I. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Black and Fakhrai

In a letter dated January 6, 1995, Drs. Keith L. Black and Habib Fakhrai of the University of California, Los Angeles, California, submitted a human gene transfer protocol entitled: A Study of the Safety of Injecting Cancer Patients with Genetically Modified Tumor Cells; Injection of Glioblastoma Patients with Irradiated Autologous Glioma Tumor Cells Genetically Modified to Express a TGF–β2 Antisense mRNA Alone or in Combination with Increasing Doses of Tumor Cells Which Have Been Genetically Modified to Secrete Interleukin-2 (IL–2): A Phase I Study to the Recombinant DNA Advisory Committee for formal review and approval during the March 6–7, 1995, meeting.

During the March 6–7, 1995, Recombinant DNA Advisory Committee meeting, a motion was made and seconded to defer the protocol submitted by Drs. Black and Fakhrai based on the lack of sufficient preclinical data. The investigators and the primary reviewers were to agree on a mutually acceptable experimental design to address the scientific questions posed by the Recombinant DNA Advisory Committee members. Once these studies have been conducted, the investigators are required to submit this data to the full Recombinant DNA Advisory Committee for review and approval. The protocol was deferred by a vote of 16 in favor, 0 opposed, and no abstentions.

On August 9, 1995, Dr. Fakhrai submitted an experimental design that was reviewed by a Recombinant DNA Advisory Committee primary reviewer.

The experimental design was found to be mutually acceptable.

On October 10, 1995, Dr. Fakhrai submitted a revised protocol entitled: A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF–β2 Antisense Gene Modified Autologous Tumor Cells to the Recombinant DNA Advisory Committee for formal review and approval during the December 4–5, 1995, meeting.

II. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Hortobagyi, Lopez-Berestein, Hung

In a letter dated July 11, 1995, Drs. Gabriel Hortobagyi, Gabriel Lopez-Berestein, and Mien-Chie Hung of the University of Texas, MD Anderson Cancer Center, Houston, Texas, submitted a human gene transfer protocol entitled: Phase I Study of E1A Gener Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpress HER–2/neu to the Recombinant DNA Advisory Committee for formal review and approval during the September 11–12, 1995, meeting.

During the September 11–12, 1995, Recombinant DNA Advisory Committee meeting, a motion was made and seconded to disapprove the protocol submitted by Drs. Hortobagyi. The motion to disapprove the protocol (absence of relevant scientific data supporting the proposed study) failed by a vote of 4 in favor, 9 opposed, and 2 abstentions. Another motion was made and seconded to accept the protocol contingent on review and approval by a subcommittee of the Recombinant DNA Advisory Committee of a revised experimental design and additional preclinical data derived from additional experiments. A friendly amendment was made and accepted that the protocol be deferred pending review and approval by the full Recombinant DNA Advisory Committee of the revised experimental design and subsequent data derived from these experiments. The amended motion to defer was contingent on full Recombinant DNA Advisory Committee review of: (1) a revised experimental design (particularly relating to specific anatomical sites), (2) quantitative assessment of *ex vivo* transduction rate, (3) data demonstrating the level of sensitivity of *in vitro* assays, and (4) a revised Informed Consent document. The motion passed by a vote of 13 in favor, 1 opposed, and 1 abstention.

On October 9, 1995, Dr. Hortobagyi submitted a revised protocol to the Recombinant DNA Advisory Committee for formal review and approval during the December 4–5, meeting.

III. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Dr. Batshaw

In a letter dated October 9, 1995, Dr. Mark Batshaw, Institute for Human Gene Therapy, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, submitted a human gene transfer protocol entitled: A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency to the Recombinant DNA Advisory Committee for formal review and approval during the December 4–5, meeting.

IV. Proposed Amendments to the NIH Guidelines Regarding Semiannual/Annual Data Reporting

In a letter dated June 16, 1995, Dr. Gary Nabel outlined the redundant and onerous reporting requirements of multiple Federal agencies and local institutions. At a minimum, amending the NIH Guidelines to accommodate annual data reporting requirements rather than semiannual reporting requirements should greatly reduce the burden currently placed on principal investigators of human gene transfer protocols.

In a letter dated August 16, Ms. Debra Knorr, NIH Office of Recombinant DNA Activities, submitted to the Recombinant DNA Advisory Committee the intent to submit proposed amendments to the NIH Guidelines regarding annual data reporting. During the September 12, 1995, Recombinant DNA Advisory Committee meeting, Dr. LeRoy Walters, Chair, invited members of the Recombinant DNA Advisory Committee and the public to provide comments on the proposed amendments. No comments on the proposed amendments have been submitted to the Office of Recombinant DNA Activities to date.

The proposed amendments read as follows:

''Section IV–B–4–e–(5) currently reads:

''Section IV–B–4–e–(5). Comply with semiannual data reporting and adverse event reporting requirements for NIH and FDA-approved human gene transfer experiments (see Appendix M–VIII, Reporting Requirements—Human Gene Transfer Protocols).''

Section IV–B–4–e–(5) is amended to read:

''Section IV–B–4–e–(5). Comply with annual data reporting and adverse event reporting requirements for NIH and FDA-approved human gene transfer experiments (see Appendix M–VIII, Reporting Requirements—Human Gene Transfer Protocols).''

Section IV–C–3–c currently reads:

''Section IV–C–3–c. Administering the semiannual data reporting requirements (and subsequent review) for human gene transfer experiments, including experiments that are reviewed solely by the FDA (see Appendix M–VI, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review);''

Section IV–C–3–c is amended to read.

''Section IV–C–3–c. Administering the annual data reporting requirements (and subsequent review) for human gene transfer experiments, including experiments that are reviewed solely by the FDA (see Appendix M–VI, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review);''

Appendix M–VII currently reads:

''Appendix M–VII. Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review

''A proposal submitted under one of the following categories may be considered exempt from RAC review unless otherwise determined by NIH/ORDA and the FDA on a case-by-case basis (see Appendix M–VI–A, Categories of Human Gene Transfer Experiments that Require RAC Review).

''Note: In the event that the submitted proposal is determined to be exempt from RAC review, the documentation described in Appendices M–I through M–V will be maintained by NIH/ORDA for compliance with semiannual data reporting and adverse event reporting requirements (see Appendix M–VIII, Reporting Requirements—Human Gene Transfer Protocols). Any subsequent modifications to proposals that were not reviewed by the RAC must be submitted to NIH/ORDA in order to facilitate data reporting requirements.''

Appendix M–VII is amended to read:

''Appendix M–VII. Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review

''A proposal submitted under one of the following categories may be considered exempt from RAC review unless otherwise determined by NIH/ORDA and the FDA on a case-by-case basis (see Appendix M–VI–A, Categories of Human Gene Transfer Experiments that Require RAC Review).

''Note: In the event that the submitted proposal is determined to be exempt from RAC Review, the documentation described in Appendices M–I through M–V will be maintained by NIH/ORDA for compliance with annual data reporting and adverse event reporting requirements (see Appendix M–VIII, Reporting Requirements—Human Gene Transfer Protocols). Any subsequent modifications to proposals that were not

reviewed by the RAC must be submitted to NIH/ORDA in order to facilitate data reporting requirements.''

Appendix M–VIII–A currently reads:

''Appendix M–VIII–A. Semiannual Data Reporting

''Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) shall be required to comply with the semiannual data reporting requirements. Semiannual Data Report forms will be forwarded by NIH/ORDA to investigators. Data submitted in these reports will be evaluated by the RAC, NIH/ORDA, and the FDA and reviewed by the RAC at its next regularly scheduled meeting.''

Appendix M–VIII–A is amended to read:

''Appendix M–VIII–A. Annual Data Reporting

''Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) shall be required to comply with the annual data reporting requirements. Annual Data Report forms will be forwarded by NIH/ORDA to investigators. Data submitted in these reports will be evaluated by the RAC, NIH/ORDA, and the FDA and reviewed by the RAC at its next regularly scheduled meeting.''

V. Presentation on Ethical Issues Associated With In Utero Gene Therapy/Dr. Fletcher

Dr. John C. Fletcher, Kornfeld Professor and Director of the Center for Biomedical Ethics, University of Virginia, Charlottesville, Virginia, will be giving a presentation concerning the ethical issues associated with the proposed use of in utero gene therapy.

VI. Proposed Discussion Regarding NIH Purview of Human Gene Transfer Experiments

In a letter dated November 2, 1995, Ms. Debra Knorr proposed a discussion regarding NIH purview of human gene transfer experiments for the December 4–5, 1995, Recombinant DNA Advisory Committee meeting. Analysis of human gene transfer oversight will be discussed in the context of the following:

1. The September 8, 1995, recommendations of the NIH RAC Ad Hoc Review Committee—Inder Verma, Ph.D., Chair;

2. Data Management—maintaining public accountability relevant to human gene transfer experiments; and

3. Factors to consider in implementation of streamlined review procedures.

The NIH Director defined a number of issues relevant to the development of the field of human gene therapy, including the quality of science, the fiscal resource being devoted to the field, the role of industry in the development of clinical trials, and the disparity between scientific accomplishments and the public perceptions of human gene therapy. As a result, Dr. Varmus established two separate ad hoc advisory committees to evaluate the field of human gene therapy research.

The Ad Hoc RAC Review Committee, chaired by Inder Verma, Ph.D., was charged with providing a comprehensive assessment of past and current RAC activities in an effort to develop recommendations regarding the future role of the RAC relevant to human gene transfer experiments. The September 8, 1995, Ad Hoc RAC Review Committee recommendations are included as follows:

''Dr. Harold Varmus, Director, National Institutes of Health, appointed an ad hoc review committee to review the activities of the NIH Recombinant DNA Advisory Committee (RAC). The Director asked the committee to provide recommendations about the changing role of the RAC, the ways it may need to modify its operations, and how it should function to coordinate and facilitate productive gene therapy research.

''The committee finds that:

''1. Gene therapy represents a special development in medical research because of its potential for modification of the human genome and for the creation and dissemination of novel transmissible pathogenic vectors. In addition, there is the possibility of controversial extensions of this work, such as modification of the germline or the use of gene transfer for enhancement purposes. Thus gene therapy differs in major ways from other clinical technologies in use or under development and is, therefore, deserving of continued public scrutiny.

''2. The RAC has served—and continues to serve—several important purposes for the scientific community, patients, and the general public. In particular, by focusing its attention on the emerging field of gene therapy research and helping to set appropriate scientific safety and informed consent guidelines for investigators. As a public forum of discussion, RAC has provided an enormous service not only to the general public, researchers at academic and similar institutions and within the biotechnology industry, but also to officials at the Food and Drug Administration (FDA). In addition, RAC continues to be a credible forum for airing a wide range of public concerns about this emerging field of medical research.

''Based on these findings, the committee recommends that:

''1. To avoid duplication of effort and unnecessary delay, RAC should no longer carry out case by case review of every clinical gene transfer protocol. This function is carried out by the FDA, which is required by statute to review all such protocols before approval.

''2. Review of protocols by the RAC in an open public forum should continue in several areas of concern in which a particular protocol or new technology represents a significant degree of departure from familiar practices. Such departures include, but are not limited to, the use of novel vectors, particularly in cases in which modified human pathogens (such as herpes viruses or lentiviruses) are being evaluated; gene transfer in utero, potential germ line modification, and other similar manipulations; and gene transfer in normal volunteers. In addition, review of protocols by the RAC is warranted in other situations which could lead to the formulation of significant new policy.

''3. The RAC should define the criteria and work out procedures for identifying specific protocols requiring public review.

''4. The RAC should continue to provide advice on policy matters revolving around gene therapy and other recombinant DNA issues to the NIH Director, individual members of the research community, institutional review boards, and the public. Moreover, that critical function should be extended, enabling RAC explicitly to provide advice and recommendations on policy matters to FDA. However, the committee recommended against reconstituting RAC or a comparable advisory body within the FDA, pointing out that several important policy functions of RAC are outside the mission of that agency.

''5. A mechanism should be devised to enable ORDA, NIH and the RAC to continue to be provided with the data needed for monitoring clinical gene transfer protocols. Hence, the committee recommends that the NIH Director urge the FDA Commissioner to exempt the broad area of gene therapy from many of the proprietary restraints reserved for ordinary therapeutic drug products and biologics that come under FDA review. Such a broad exemption, similar to the one now in place for products being developed for the treatment of individuals infected with HIV, would greatly expedite efforts to monitor and evaluate gene transfer protocols and,

ultimately, would accelerate progress in the clinical application of gene therapy.''

The Panel to Assess NIH Investment in Gene Therapy Research, chaired by Stuart J. Orkin, M.D. and Arno G. Motulsky, M.D., is charged with evaluating the current status of NIH-funded (directly and indirectly) gene therapy clinical trials and developing recommendations regarding future NIH investment in gene therapy research. The panel is currently preparing its recommendations which will be presented at the December 1995 Director's Advisory Committee meeting.

NIH invites written comments from industry, patient advocacy groups, other Federal agencies, and other interested parties.

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Effective Date: November 8, 1995.

Lana Skirboll,

Associate Director for Science Policy.

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